REMARKS

Claims 1-58 are pending in the application.

Claim 53 has been amended to introduce a space between "phosphate" and "ester" in the last compound, "di-hydroxylamine-benzylphosphate ester", in order to address the objection to claim 53 on page 5 of the Office Action.

No other amendments have been introduced.

Rejections under 35 U.S.C. § 103

Claims 1-58 were previously rejected as allegedly obvious over Krishna et al. ("Kirshna"). On page 5 of the current Office Action, the Examiner now rejects claims 1-58 as allegedly unpatentable over Krishna in view of Schmidl et al. in U.S. Patent No. 5,504,072 ("Schmidl"). The Examiner does not expressly indicate that the rejection of claims 1-58 over Krishna only is maintained. Applicants note that on page 8 of the Office Action, Schmidl is characterized by the Examiner as teaching the pharmaceutical administration of vitamins, minerals carbohydrates, proteins, and amino acids, namely carnitine. The Examiner appears to be using Schmidl as a secondary reference applied only to those claims that read on a pharmaceutical composition comprising a primary N-hydroxylamine and carnitine ("Since carnitine and nitroxide compounds are shown to have advantageous properties to an individual, the skilled artisan would be motivated to combine them together for administration." page 9 of the Office Action). Accordingly, the rejection over Krishna in view of Schmidl would only appear to apply to claim 55. Applicants respectfully request clarification of this rejection.

The rejection does not establish a proper case of prima facie obviousness.

The Examiner contends that one of skill would have been motivated to use primary N-hydroxylamines as a pharmaceutical composition based on the teachings in Krishna with regard to secondary hydroxylamines. Applicants have traversed the rejection of claims 1-58 over Krishna for reasons of record.

In brief, Krishna evaluates the effects of changes in the ring structure on antioxidant activity of cyclic nitroxides and their corresponding N-hydroxylamines. Krishna teaches the importance of "stable nitroxides" and their secondary hydroxylamine and amine precursors (see, e.g., Abstract, line 1; page 3477, column 2, line 24; page 3478, column 1, lines 28 and 44; and page 3480, column 2, line 25). The Examiner proposes that one of skill would choose to substitute one of the two carbon moieties of the secondary hydroxylamines in Krishna with a hydrogen. However, the Examiner's proposed modification does not logically follow from the emphasis in Krishna on the ability of stable cyclic nitroxides to act as antioxidants.

Further, Krishna focuses on evaluating the effect of changes in ring structure on antioxidant activity. Applicants' invention is based on the importance of the primary N-hydroxylamine functional group, which does not cyclize. In order to arrive at Applicants' invention, one of skill would have to replace the very moieties that Krishna was studying with hydrogen. Accordingly, there is no proper motivation to modify Krishna.

The disclosure in Schmidl does not compensate for the deficiencies in Krishna. The rejection therefore does not establish a proper case of *prima facie* obviousness.

Primary N-hydroxylamines exhibit superior properties

In response to Applicants' evidence in the specification that the compositions have superior properties, the Examiner alleges that the unexpected ability of primary N-hydroxylamines to delay senescence is not sufficient to lend patentability to the claims. In particular, the Examiner cites *In re Payne* 203 USPQ 245 (CCPA 1979); *In re Wiseman* 201 USPQ 658 (CCPA), and *Ex parte Obiaya* 227 USPq 58 (Bd. Pat. App. & Int.) in support of his arguments. Applicants respectfully disagree.

As Applicants noted in the previous response, cyclic-N-hydroxlamines (R₂NOH) and their respective nitroxides protect against oxidative damage induced by H₂O₂, but do not delay cellular senescence. Primary N-hydroxylamines, however, have the superior property of delaying senescence, as taught in the specification, e.g., on page 46, lines 2-7; and page 48, lines

18-24; and page 49, lines 7-11. The facts here distinguish the present application from the cases cited by the Examiner.

In *In re Payne*, the claims at issue are drawn to chemical compounds having particular structures. The CCPA concluded that the patent office had properly established that the claimed compounds were *prima facie* obvious. However, the court also considered Appellants' evidence of unexpected or superior properties to rebut the *prima facie* case ("A *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexepectedly advantageous or superior preoprites." *In re Payne* 245, 256, citing numerous cases). Although the court found that the Appellants' evidence was insufficient, as the claimed compounds were not tested against the closest prior art, that aspect of the analysis of surprising results is not at issue in the present application. The court in *Payne* clearly recognized the relevance of surprising results to patentability. Thus, *In re Payne* in fact supports that a compound that may be structurally obvious in view of the prior art can be patentable based on its unexpected properties.

In *In re Wiseman*, the CCPA considered Appellants' arguments that the patent office had not established a proper case of obviousness. The CCPA affirmed the Patent Office's finding that the claims were obvious, noting that there must be some evidence of record by way of affidavits or clear and persuasive assertion in the specification, that the fact relied on to support patentability was the discovery of the applicants. No issues relating to the rebuttal of a *prima facie* case of obviousness based on surprising results were considered.

In Ex parte Obiaya, the claimed invention related to a sensor containing a combustion fluid and oxygen concentration analyzer in which a fluid sample was drawn into the sensor apparatus and separated into two parts, one of which went to the oxygen analyzer, the other of which went to the combustion analyzer. A heater was employed to maintain the sample going to the combustion analyzer at a constant temperature to obtain uniform results. One of the issues considered by the Board was Appellants' evidence of an unexpected result, i.e., that a shorter response time was obtained when a labyrinth heater was employed. The Board noted that the prior art references disclosing the labyrinth heater indicated that there was an advantage (i.e.,

a first advantage) obtained by using such heaters in that the samples were maintained at a uniform temperature. The Board held that the fact that the appellant recognized another advantage that would flow naturally from following the suggestion in the prior art was not a basis for patentability. However, in the present case, the Examiner has not pointed to a first advantage that the claimed compositions would allegedly have over the prior art. Again assuming arguendo that pharmaceutical compositions comprising primary N-hydroxylamines are obvious, as alleged by the Examiner, such compositions would be simple alternatives to the prior art secondary hydroxylamine compositions. Thus, there is no "first" advantage (over the prior art) in pharmaceutical compositions comprising primary N-hydroxyl amines from which a second advantage (in this case, the ability to delay senescence) would naturally flow. Accordingly, the reasoning of the Board in *Obiaya* does not apply here.

The law is clear that a *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties *In re Papeschi*, 315 F.2d281, 137 USPA43 (CCPA 1953). Further, evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a *prima facie* case of obviousness (MPEP § 2144.08.II.B, citing *In re Chupp*, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987)). Here, the facts are analogous to those of *In re Chupp*. Even though primary N-hydroxylamines may share common properties with secondary hydroxylamines, the remarkable results of the primary N-hydroxylamines in delaying senescence (compared to the lack of activity of secondary hydroxylamines in this regard) is sufficient to render the claims patentable.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

Obviousness type double patenting

Claims 1-58 were also rejected for allegedly obviousness type double patenting over claims 1-57 of co-pending application no. 10/713,432. Applicants believe that this is obviated in view of the changed status of the cited application.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted

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